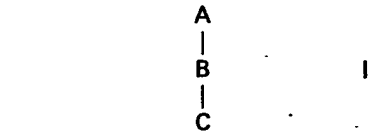
(12) UK Patent Application (19) GB (11) 2 093 450 A

(21) Application No 8204391
(22) Date of filing 15 Feb 1982
(30) Priority data
(31) 1110/81
1111/81
6480/81
(32) 19 Feb 1981
19 Feb 1981
9 Oct 1981
(33) Switzerland (CH)
(43) Application published
2 Sep 1982
(51) INT CL³
C07D 413/12 A61K
31/415 C07D 417/12
(52) Domestic classification
C2C 1173 1412 1434
1442 1532 1562 1602
200 202 213 215 220 225
226 22Y 246 247 250 251
252 255 256 25Y 28X
29X 29Y 305 30Y 311
313 314 31Y 323 326 32Y
337 339 345 351 355 360
361 364 365 36Y 456
45X 45Y 610 616 620
623 624 625 62Y 634 652
656 662 665 670 672 680
682 697 69Y 709 718 719
721 74Y 770 775 778 779
802 80Y AA LH LL MV NB
NF
(56) Documents cited
GB 1598366
GB 1598365
GB 1552163
GB 1429926
GB 1429683
(58) Field of search
C2C
(71) Applicants
Sandoz Ltd.,
35 Lichtstrasse,
CH—4002 Basle,
Switzerland
(72) Inventors
Peter Neumann,
Gerhard Bormann
(74) Agents
B. A. Yorke and Co.,
98 The Centre Feltham
Middlesex TW13 4EP

(54) 2,1,3-Benzothiadiazole and Benzoxadiazole derivatives

(57) The compounds of formula I,



wherein

A is an optionally substituted 2,1,3-benzothiadiazole or 2,1,3-benzoxadiazole moiety,
B is a trisubstituted amino group and
C is an optionally 1-substituted 4,5-dihydro-1H-imidazol-2-yl or an optionally 3-substituted 3,4,5,6-tetrahydropyrimidin-2-yl moiety,
and their salts are useful as bradycardiac, anti-tremor, anti-rigor and myotonolytic agents, tranquillizers and antidepressants.

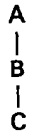
GB 2 093 450 A

SPECIFICATION

Amino-2,1,3-benzothiadiazole and -benzoxadiazole derivatives, their preparation and pharmaceutical compositions containing them

The present invention relates to amino-2,1,3-benzothiadiazole and -benzoxadiazole derivatives, their preparation and pharmaceutical compositions containing them.

In particular, the invention provides compounds of formula I



I

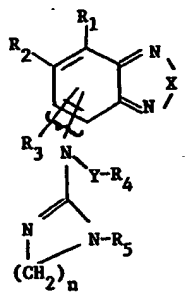
wherein

A is an optionally substituted 2,1,3-benzothiadiazole or 2,1,3-benzoxadiazole moiety,

B is a trisubstituted amino group and

C is an optionally 1-substituted 4,5-dihydro-1H-imidazol-2-yl or an optionally 3-substituted 3,4,5,6-tetrahydropyrimidin-2-yl moiety, hereinafter referred to as "the compounds of the invention".

In accordance with the invention, there are especially provided compounds of formula Ia,



Ia

wherein

n is 2 or 3,

X is oxygen or sulfur,

Y is a bond or oxygen,

R_1, R_2 and R_3 independently are hydrogen, halogen of atomic number of from 9 to 53, cyano, hydroxy, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or alkylthio of 1 to 4 carbon atoms,

R_4 is

i) alkyl of 1 to 6 carbon atoms optionally monosubstituted by hydroxy or halogen of atomic number of 9 to 53 and wherein the hydroxy or halogen moiety is separated from Y by at least 2 carbon atoms; alkenyl of 3 to 6 carbon atoms optionally monosubstituted by halogen of atomic number of from 9 to 53 and wherein the double bond and the halogen moiety are separated from Y by at least 2 carbon atoms; alkinyl of 3 to 6 carbon atoms wherein the triple bond is separated from Y by at least 2 carbon atoms; cycloalkyl of 3 to 7 carbon atoms; cycloalkylalkyl of 3 to 7 carbon atoms in the cycloalkyl moiety and of 1 to 4 carbon atoms in the alkyl moiety thereof;

ii) 2,2,5,5-tetraalkylpyrrolidin-1-ylalkyl or 2,2,6,6-tetraalkylpiperidin-1-ylalkyl independently of 1 to 4 carbon atoms in each of the alkyl moieties of the pyrrolidine or piperidine moiety, of 2 to 5 carbon atoms in the alkyl moiety bound to Y and wherein the nitrogen atom of the pyrrolidine or piperidine moiety is separated from Y by at least 2 carbon atoms; furanylalkyl, thienylalkyl or pyridylalkyl each of 1 to 4 carbon atoms in the alkyl moiety thereof; or morpholin-1-ylalkyl of 2 to 5 carbon atoms in the alkyl moiety thereof and wherein the nitrogen atom of the morpholine moiety is separated from Y by at least 2 carbon atoms;

iii) phenylalkyl of 7 to 11 carbon atoms, phenoxyalkyl of 8 to 12 carbon atoms wherein the oxygen atom is separated from Y by at least 2 carbon atoms, phenylcarbonylalkyl of 8 to 12 carbon atoms, phenylalkoxyalkyl of 1 to 4 carbon atoms in the alkoxy and of 2 to 5 carbon atoms in the alkyl moiety thereof and wherein the oxygen atom is separated from Y by at least 2 carbon atoms, phenylalkyl of 9 to 13 carbon atoms wherein the double bond is separated from Y by at least 2 carbon atoms, phenylalkinyl of 9 to 13 carbon atoms wherein the triple bond is separated from Y by at least 2 carbon atoms, all the phenyl rings in the six above-mentioned substituents optionally being mono- or independently di-substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 53 or, when Y is a bond, alternatively or additionally also by hydroxy; or

iiii) when Y is oxygen, additionally hydrogen and R_5 is hydrogen or alkyl of 1 to 4 carbon atoms.

It is to be appreciated that the compounds of the invention are defined with reference to one specific tautomeric form, e.g. that of formula Ia, only for the sake of simplicity. However, the invention

extends to all tautomeric forms of th compounds of formula Ia.

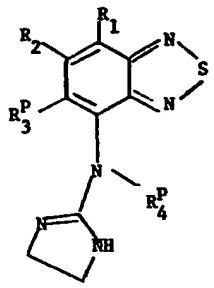
It is also to be appreciated that any carbon chain of more than 2 carbon atoms may be branched or straight-chained.

Alkyl of 1 to 4 carbon atoms or f 1 to 6 carbon atoms and/or alkoxy and/or alkylthio preferably are of 1 or 2, sp cially of 1 carbon atom. Halog n preferably is chlorin or bromin , especially chlorine. When alkyl of 1 to 6 carbon atoms is substituted by hydroxy, it is especially substituted in the ω-position. Alkenyl is preferably of 3 or 4 carbon atoms, it especially is allyl. When it is substituted by halogen, it preferably is substituted at a carbon atom bound to the double bond; it is then especially 2-chloro-2-propenyl. Alkinyl preferably is of 3 or 4 carbon atoms; it especially is 2-propinyl. Cycloalkyl preferably is of 3,5 or 6 carbon atoms; it especially is cyclopentyl. Cycloalkylalkyl preferably is of 3, 5 or 6, especially of 3 carbon atoms in the cycloalkyl moiety thereof and preferably of 1 or 2, especially of 1 carbon atom in the alkyl moiety thereof. In 2,2,5,5-tetraalkylpyrrolidin-1-ylalkyl and 2,2,6,6-tetraalkylpiperidin-1-ylalkyl the alkyl substituents preferably are methyl or ethyl, especially methyl; they preferably are identical; the bridging alkylene moiety preferably is ethylene. Furanylalkyl preferably is furanylmethyl, especially 2-furanylmethyl. Thienylalkyl preferably is thienylmethyl, especially 2-thienylmethyl. Pyridylalkyl preferably is pyridylmethyl, especially 2- or 3-, especially 2-pyridylmethyl. Morpholin-1-ylalkyl preferably is morpholin-1-ylethyl. Phenylalkyl preferably is benzyl or phenethyl, optionally substituted. Phenoxyalkyl preferably is phenoxyethyl, optionally substituted. Phenylalkoxy preferably is benzyloxyethyl, optionally substituted. Phenylalkenyl preferably is cinnamyl, optionally substituted. Phenylalkinyl preferably is 3-phenyl-2-propinyl, optionally substituted.

When a phenyl ring as part of a substituent R_4 is substituted, it preferably is substituted in the para position. When it is disubstituted, it preferably is substituted in the meta and para positions. The substituents preferably are identical. Preferred as substituents are halogen, alkyl and alkoxy, especially alkoxy.

n preferably is 2. X preferably is sulfur. Y preferably is a bond. R_1 and/or R_2 preferably are hydrogen, halogen, alkyl, alkoxy or cyano, especially hydrogen. They preferably are identical when they both are other than hydrogen. R_3 preferably is hydrogen, hydroxy, alkyl, alkoxy or halogen, especially halogen. The nitrogen atom carrying Y—R_4 preferably is bound at the 4 position of the 2,1,3-benzothiadiazole or 2,1,3-benzoxadiazole ring. R_4 preferably has the above-defined significance i) or iii), especially significance i). R_5 preferably is hydrogen. Significance i) preferably is alkyl optionally substituted by hydroxy, especially alkyl, or is alkenyl or cycloalkylalkyl, it especially is alkenyl. The above-defined significance ii) preferably is morpholinylalkyl. Significance iii) preferably is optionally substituted phenylalkyl, phenoxyalkyl, phenylalkoxyalkyl or phenylalkenyl.

One group of compounds of the invention is the compounds of formula Ipa



Ipa

wherein

R_1 and R_2 are as defined above,

R_3^p has the significance indicated above for R_3 and

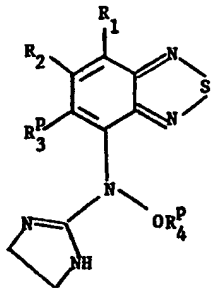
R_4^p is

i) alkyl of 1 to 6 carbon atoms; alkenyl of 3 to 6 carbon atoms wherein the double bond is separated from the nitrogen atom by at least 2 carbon atoms; 2-chloro-2-propenyl; alkinyl of 3 to 6 carbon atoms wherein the triple bond is separated from the nitrogen atom by at least 2 carbon atoms; cycloalkyl of 3 to 7 carbon atoms; cycloalkylalkyl of 3 to 6 carbon atoms in the cycloalkyl moiety and of 1 to 4 carbon atoms in the alkyl moiety thereof, the total number of carbon atoms not exceeding 7;

ii) thienylmethyl, 2-furanylmethyl or pyridylmethyl; or

iii) benzyl or cinnamyl.

A further group of compounds of the invention is the compounds of formula Ipb



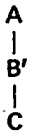
Ipb

wherein

R_1, R_2, R_3^p and R_4^p are as defined above.

A compound of the invention may be obtained by a process comprising

a) appropriately substituting a corresponding compound of formula II

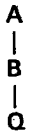


II

wherein

A and C are as defined above and B' is a secondary amino group or

b) reacting a corresponding compound of formula III



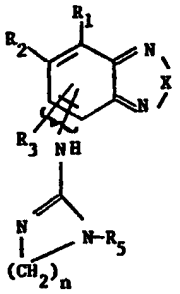
III

wherein

A and B are as defined above and Q is a group capable of cyclization with a diamine, with a corresponding, optionally 1-substituted ethylene or propylene diamine.

In particular, a compound of formula Ia may be obtained by

a) appropriately substituting the bridging nitrogen atom in a corresponding compound of formula IIa

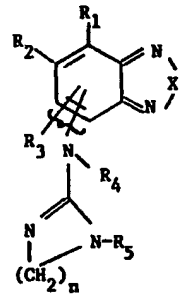


IIa

wherein

n, X, R_1, R_2, R_3 and R_5 are as defined above or

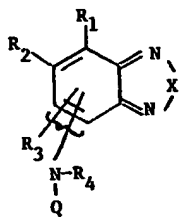
b) for the production of a compound of formula Iaa,



Iaa

wherein

n, X and R_1 and R_5 are as defined above, reacting a corresponding compound of formula IIIa



IIIa

wherein

Q, X and R_1 to R_4 are as defined above, with a corresponding compound of formula IV

$$H_2N—(CH_2)_n—NHR_5 \qquad IV$$

wherein

n and R_5 are as defined above.

Process variant a) may be effected in conventional manner for the production of analogous trisubstituted amines by substitution of a secondary amine.

For the production of a compound wherein the substituent to be introduced is to be bound to the nitrogen atom over a carbon atom, the reaction conditions of an N-alkylation of a secondary amine may be used.

An appropriate N-alkylating agent is e.g. a compound of formula $Z—R_4$ wherein R_4 is as defined above and Z is a leaving group, e.g. halogen or a group $R_z—SO_2—O—$, wherein R_z is phenyl, tolyl or lower alkyl. Z especially is bromine or chlorine. The reaction is conveniently effected in an organic solvent such as dimethylformamide or an alcohol. Preferably a basic condensation agent such as sodium carbonate, pyridine or N-ethyl-N,N-diisopropylamine is used. The reaction temperature may vary between room temperature and approximately 100°C.

For the production of a compound wherein the substituent to be introduced is to be bound to the nitrogen atom over an oxygen atom, the reaction preferably is effected in two stages, e.g. as follows:

In a first stage, a compound of formula II is substituted at the secondary amino group with hydroxy. To this effect a compound of formula II is oxidized with an oxidizing agent such as 3-chloroperbenzoic acid. Conveniently an inert solvent such as methylene chloride is used. The reaction preferably is effected at a temperature from about 0° to about 25°C. A corresponding compound substituted at the nitrogen atom by hydroxy is obtained.

In a second stage, if required, the resultant hydroxy compound is then O-alkylated. Conveniently, reaction conditions similar to those indicated above for N-alkylation may be used. Preferably strongly alkaline conditions, as e.g. in the presence of sodium ethylate, are used.

The reactivities of any substituents present should be taken into account. Thus, when the 2,1,3-benzothiadiazole or 2,1,3-benzoxadiazole ring is substituted e.g. by hydroxy, it may be indicated to effect the above-mentioned oxydation and O-alkylation with the phenolic hydroxy group or groups in protected form, and to deprotect thereafter. Methyl is an example of a phenolic hydroxy protecting group. It may be split off e.g. with trimethylsilyl iodide or the lithium salt of ethyl mercaptan. When R_4 is phenylcarbonylalkyl the carbonyl moiety may also be temporarily protected e.g. in the form of a 1,3-dioxolane ring.

Process variant b) may also be effected in conventional manner for the production of analogous 2-amino-4,5-dihydro-1H-imidazoles or 2-amino-3,4,5,6-tetrahydropyrimidines.

Q is e.g. cyano, $—C(NH_2)=NH$, —C(SAlk)=NH or —C(OAlk)=NH wherein Alk is lower alkyl, preferably methyl, or is e.g. —COOAlk', wherein Alk' is lower alkyl, preferably ethyl. Q especially is cyano.

The reaction preferably is effected in an inert organic solvent, e.g. an alcohol of 3 to 8 carbon atoms such as n-pentanol or a hydrocarbon such as xylol. The reaction preferably is effected in the presence of an excess of a monovalent salt of the ethylene or propylene diamine. When a large excess of the diamine in free base form is used, then it may also serve as a solvent. The reaction temperature is about 50° to about 200°C, preferably about 110° to about 150°C.

The compounds of the invention may be isolated from the reaction mixture and purified in a manner analogous to known methods.

The compounds of the invention may exist in free form, normally as a base, or in salt form. Free forms may be converted into salt forms in conventional manner and vice-versa. Suitable acids for acid addition salt formation include hydrochloric, malonic, p-toluene-sulfonic and methan sulfonic acid. Suitable bases for anionic salt formation, e.g. when R_1, R_2 and/or R_3 is hydroxy, include sodium and potassium hydroxide.

The starting materials may be obtained in known manner.

A compound of formula IIIa wherein Q is cyano may e.g. be obtained by appropriately substituting the bridging nitrogen atom in a corresponding N-cyano-2,1,3-benzothiadiazol- or N-cyano-2,1,3-benzoxadiazol-4-amine.

Insofar as the preparation of any particular starting material is not particularly described, this may be effected in conventional manner or in analogous manner to that described herein.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

EXAMPLE 1

N-allyl-5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine (process variant a)

38 g Allyl bromide are added to a solution of 20 g 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine in 500 ml methanol, 20 ml dimethylformamide and 9 ml pyridine. The mixture is stirred and heated for 19 hours under reflux, and then the pale yellow solution evaporated under reduced pressure. The residue is stirred in water and the resulting crystalline hydrobromide of the title compound filtered and washed with cold water. The solution is made alkaline with 20% sodium hydroxide, and the free base extracted with methylene chloride. The organic phase is dried with sodium sulfate and the solvent evaporated. The residue is recrystallized from ethyl acetate. The title compound is obtained (M.P. of the free base form 140—142°; M.P. of the hydrochloride salt form 218—219°).

EXAMPLE 2

5-chloro-N-hydroxy-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine (process variant a)

To a stirred suspension of 7.5 g 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine in 600 ml of methylene chloride are added at 5° over 20 minutes 7.5 g of m-chloroperbenzoic acid. The solution is stirred for 10 minutes at room temperature and then extracted successively with 60 ml and twice 30 ml of 2N sodium hydroxide. The combined extract are then acidified with 1N aqueous hydrochloric acid solution. The precipitated m-chloroperbenzoic acid is filtered off, the solvent evaporated to dryness, the residue dissolved in 500 ml ethanol, the precipitated sodium chloride filtered off, the filtrate treated with charcoal and the solvent evaporated to dryness. The residue is recrystallized from isopropanol. The title compound is obtained (M.P. of the hydrochloride salt form 220—222° [dec.]).

EXAMPLE 3

5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-N-(2-phenoxyethoxy)-2,1,3-benzothiadiazol-4-amine (process variant a)

5 g 5-chloro-N-hydroxy-N(4,5-dihydro-1H-imidazol-2-yl-2,1,3-benzothiadiazol-4-amine hydrochloride (obtained according to Example 2 above) are added to a solution of 0.68 g sodium in 70 ml ethanol followed by 3.77 g 2-bromoethyl phenyl ether. The mixture is stirred for 2 hours at room temperature. The resulting precipitate is filtered off and the filtrate evaporated under reduced pressure. The residue is dissolved in methylene chloride and washed with 1N hydrochloric acid. The organic phase is dried with sodium sulfate and the solvent evaporated. The title compound is obtained (M.P. of the hydrochloride salt form 161—162°).

EXAMPLE 4

N-allyl-5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine (process variant b)

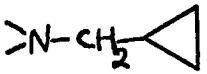
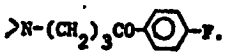
9.5 g toluene sulfonic acid monohydrate and 3 g ethylene diamine are dissolved in 3 ml water and reacted with a solution of 2.5 g N-allyl-5-chloro-N-cyano-2,1,3-benzothiadiazol-4-amino in 10 ml xylol. The mixture is heated 4 hours under refluxing; after cooling 100 ml of 2N hydrochloric acid solution are added and the mixture is extracted twice with 60 ml methylene chloride. The aqueous phase is treated with charcoal, made alkaline with concentrated aqeuous ammonia solution and then extracted with methylene chloride. The organic phase is dried and the solvent evaporaed. The residue is recrystallized from ethyl acetate. The title compound is obtained (M.P. of the free base form 140—142°; M.P. of the hydrochloride salt form 218—219°).

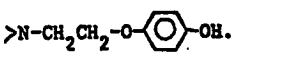
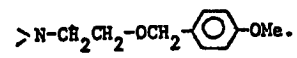
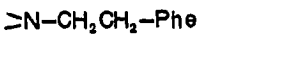
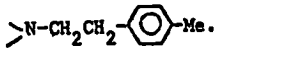
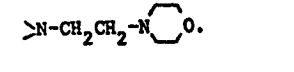
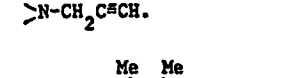
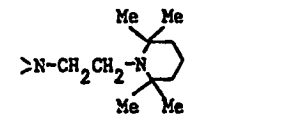
The starting material is obtained as follows: 5 g 5-chloro-N-cyano-2,1,3-benzothiadiazol-4-amine are added to a solution of 0.55 g sodium in 60 ml ethanol and the mixture is reacted with 3 g allyl bromid . The mixture is agitated 3 hours under refluxing and the solvent evaporated under vacuum. The residue is extract d with m thylene chlorid . N-allyl-5-chloro-N-cyano-2,1,3-benzothiadiazol-4-amin (M.P. 62—63°) is obtain d.

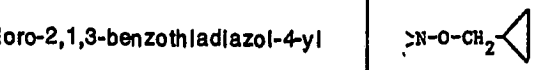
The following compounds of formula I may be obtain d in an analogous mann r by appropriat substitution of a corresponding compound of formula II wherein B′ is

(process variant a) or by reaction of a corresponding compound of formula III wherein Q is cyano with a corresponding ethylen or propylene diamine (process variant b):

Example Nr.	Analogous to Ex. No.	A	B	C	M.P.
I) N–C–bond					
5	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–Me	4,5-dihydr-1H-imidazol-2-yl	b 128–131°
6	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–Me	4,5-dihydro-1H-1-methylimidazol-2-yl	b 165–185°
7	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–Et	4,5-dihydro-1H-imidazol-2-yl	b 132–135°
8	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–Bz	4,5-dihydro-1H-imidazol-2-yl	b 132–134°
9	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N-crotyl	4,5-dihydro-1H-imidazol-2-yl	b 151–154°
10	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–CH_2C(Me)=CH_2	4,5-dihydro-1H-imidazol-2-yl	b 131–134°
11	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–CH_2C(Cl)=CH_2	4,5-dihydro-1H-imidazol-2-yl	b 139–141.5°
12	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–CH_2CH=CMe_2	4,5-dihydro-1H-imidazol-2-yl	b 112–114°
13	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–CH_2CH=CH–Phe	4,5-dihydro-1H-imidazol-2-yl	b 136–140°
14	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–iPr	4,5-dihydro-1H-imidazol-2-yl	b 138–141°
15	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–iBu	4,5-dihydro-1H-imidazol-2-yl	b 154°

Example No.	Analogous to Ex. No.	A	B	C	M.P.
16	1 and 4	5-chloro-7-methyl-2,1,3-benzothiadiazol-4-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 153–157°
17	1 and 4	4-methyl-2,1,3-benzothiadiazol-5-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 122–124°
18	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N-allyl	4,5-dihydro-1H-1-methylimidazol-2-yl	b 108–110°
19	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	b 165–167°
20	1 and 4	4-bromo-2,1,3-benzothiadiazol-5-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 143–147°
21	1 and 4	7-chloro-5-methyl-2,1,3-benzothiadiazol-4-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 162–165°
22	1 and 4	5-methyl-2,1,3-benzothiadiazol-4-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 127–130°
23	1 and 4	5-methyl-2,1,3-benzoxadiazol-4-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 125–127°
24	1 and 4	5,7-dimethyl-2,1,3-benzoxadiazol-4-yl	>N–allyl	4,5-dihydro-1H-imidazol-2-yl	b 161–164°
25	1* and 4**	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	ta 201–203°
26	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–CH_2CH_2–O–Phe	4,5-dihydro-1H-imidazol-2-yl	hfu 175–178°

Example Nr.	Analogous to Ex. No.	A	B	C	M.P.
27	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	fu 276–278°
28	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	hfu 161–163°
29	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	hfu 217–218°
30	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	br 262–264°
31	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	hfu 221–223°
32	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	fu 185–187°
33	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	hfu 210–211°
34	1 and 4	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	fu 255–257°
II) N–O–bond					
35	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	≥N–O–allyl	4,5-dihydro-1H-imidazol-2-yl	b 136–138°

Example No.	Analogous to Ex. No.	A	B	C	M.P.
36	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–O–Me	4,5-dihydro-1H-imidazol-2-yl	b 127–129°
37	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl		4,5-dihydro-1H-imidazol-2-yl	b 118–120°
38	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–O–CH_2C≡CH	4,5-dihydro-1H-imidazol-2-yl	ch 183° (dec.)
39	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–O–CH_2C(Me)=CH_2	4,5-dihydro-1H-imidazol-2-yl	hfu 146–147°
40	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–O–CH_2CH=CHCH$_3$	4,5-dihydro-1H-imidazol-2-yl	hfu 155–156°
41	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–O–CH_2CH=CH–Phe	4,5-dihydro-1H-imidazol-2-yl	hfu 178–179°
42	2 + 3	5-chloro-2,1,3-benzothiadiazol-4-yl	>N–O–CH_2CH_2OH	4,5-dihydro-1H-imidazol-2-yl	hfu 144–146°

*The substitution reaction of 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine may also be effected with 4-chloro-p-fluorobutyrophenone in protected form, i.e. wherein the keto moiety is protected in the form of a 1,3-dioxolone-2-yl moiety and the resultant compound may thereafter be deprotected using dilute aqueous hydrochloric acid solution.

**The cyclization reaction may also be effected with the starting compound having the keto moiety in the p-fluorobutyrophenone group protected in the form of a 1,3-dioxolone-2-yl moiety and the resultant compound may thereafter be deprotected using dilute aqueous hydrochloric acid solution.

M.P. = melting point
dec. = decomposition

b = in free base form
br = in hydrobromide acid addition salt form
ch = in hydrochloride acid addition salt form
fu = in fumarate acid addition salt form
hfu = inhydrogen fumarate acid addition salt form
ta = in acid addition salt form as tartrate

iBu = isobutyl
Bz = benzyl
Et = ethyl
Me = methyl
Phe = phenyl
iPr = isopropyl

The compounds of the invention exhibit pharmacological activity in animals.

In particular, the compounds possess bradycardiac activity, as indicated by standard tests. For example, in the spontaneously-beating right ventricle of the guinea pig (method of Dixon, A. K. et al., *Arzneim. F.* 27 [1977] 1968—1979) a decrease in the heart rate is observed at a bath concentration of from about 1 μM to about 100 μM.

In the pithed rat preparation (method of H. Kleinlogel et al., *Europ. J. Pharmacol. 33* [1975] 159—163) the compounds exhibit heart rate decreasing activity at a dosage of about 0.3 to about 10 mg/kg i.v.

The compounds are devoid of peripheral α-mimetic activity, as evidenced by the observation that the bradycardiac activity is not accompanied by any significant vasoconstriction or blood pressure increase.

The compounds of the invention are therefore indicated for use as bradycardiac agents, e.g. for the prophylaxis and treatment of cardiac disorders such as Angina pectoris or heart rhythm disturbances such as sinus tachycardia.

Preferred in this indication are the compounds of Examples 1, 3, 10, 15, 19, 23, 28, 30 and 41, especially of Examples 1, 3 and 10, particularly of Example 1.

Additionally, some of the compounds, in particular those of formula Ia wherein Y is oxygen, exhibit a pronounced degree of membrane-stabilizing activity which may make them particularly useful in the treatment of heart rhythm disturbances not necessarily related to a sinus tachycardia.

An indicated daily dosage is from about 5 mg to about 100 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 1.25 mg to about 50 mg, or in sustained release form.

The compounds of the invention additionally exhibit anti-tremor activity, as indicated by standard tests. This appears from a tremor antagonism in mice on p.o. administration of from about 10 to about 100 mg/kg animal body weight of the compounds in accordance with the following test:

The evening before the test day the mice used for the test (50% males and 50% females) are deprived of feed. Groups of ten animals each are used for the test, one group forming the control group. The compound to be tested is administered to the animals in each group, the doses increasing from group to group. A physiological saline solution is given to the animals of the control group. 30 minutes after administration of the compound to be tested, 100 mg/kg animal body weight of a tremor-producing compound (2,6-dichlorophenyl-acetimidoyl ureide) is administered p.o. to all the animals. 5, 10, 15 and 20 minutes after administration of the tremor-producing compound the animals are judged in accordance with the following scale: 2 = strong tremor; 1 = weak tremor; 0 = no tremor. Evaluation is then effected: for the three first measurements (5, 10 and 15 minutes after administration), the behavour of each mouse is determined, and the group average values are estimated as follows:

group with strong tremor = averages 1.5—2.0
group with weak tremor = averages 0.5—1.5
group with tremor = averages 0—0.5

The compounds of the invention are therefore indicated for use as anti-tremor agents.

The compounds also exhibit anti-rigor activity, as indicated by standard tests. This appears from a rigor antagonism in rats on i.v. administration of from about 0.001 to about 10 mg/kg animal body weight of the compounds, in accordance with the following test:

Rats are injected i.p. with 7.5 mg/kg animals body weight of Thalamonal (Registered Trade Mark), whereupon these animals develop a rigor which can be measured with an electromyograph. The dose of active compound which must be injected i.v. in order to inhibit the rigor of the rats is then ascertained.

The compounds are therefore further indicated for use as anti-rigor agents.

The compounds of the invention also exhibit myotonolytic activity, as indicated by standard tests. For example, in rabbits on i.v. administration of from 0.001 to 0.1 mg/kg animal body weight of the compounds a significant muscle relaxing effect is observed in accordance with the method of Teschendof et al., *Arch. Exp. Pharmacol. 266,* 467—468 (1970).

The compounds are therefore further indicated for use as myotonolytics, for example for the treatment of spastic conditions of different etiology (neurological, inflammatory, rheumatic, etc.) and muscle relaxants.

The compounds also exhibit tranquillizing and sedating activity, as indicated by standard tests. Thus, the compounds suppress motility, as can be demonstrated in mice. In one test two groups, each comprising four mice (one group as a control group), administered with 0.01 mg/kg to 1.0 mg/kg p.o. of the test compound is placed in a cage in redlight (Electronic Motility Testing obtainable from Motron-Producter, Stockholm, Sweden). The number of times the mice interrupt the light beams is counted electronically every fifteen minutes over a period of 60 minutes. Furthermore, the compounds reduced defensive ambivalence behaviour (a form of conflict behaviour) and increase social contact in standard animal introduction tests. In one test a male mouse administered with 0.1 to 1 mg/kg p.o. of the compound is placed for 6 minutes into the home cage of an isolated, aggressive male mouse. The behaviour of the introduced mouse is then statistically analysed according to the method of A. K. Dixon

and J. H. Mackintosh, *Anim. Behav. 19,* 138—140 (1971) using the behavioural categories outlined by A. K. Dixon "Rodent Social Behaviour in Relation to Biomedical Research" in "Das Tier im Experiment", Ed. W. Wiehr, Hans Huber Verlag, Bern 1978, e.g. nonsocial activity, social investigation and mating, aggression, defensive ambivalence, fleeing or retreating and feeding behaviour. Furthermore, on administration of 0.3 to 3 mg/kg p.o. of the compounds to rats in the sleep/wake cycle carried out in accordance with the principles of H. Kleinlogel et al., *European J. Pharmacol. 33,* 159—163 (1975) an increase of dozing is observed. The EEG is recorded over 8 hours.

The compounds are therefore indicated for use as tranquillizers and sedatives.

The compounds also exhibit antidepressive activity as indicated by standard tests. Thus, an inhibition of tetrabenazine-induced catalepsy and ptosis in rats is observed upon intraperitoneal administration of from 5 to 20 mg/kg animal body weight of the compounds in accordance with the method described by Stille (*Arzneimittel-Forsch.* [1964] *14,* 534). Furthermore, the compounds on administration of from 1 to 30 mg/kg i.p. to mice reduce the immobility induced by water-immersion according to the method described by R. D. Porsolt et al., *Arch. Int. Pharmacodyn. 229* 327—336 (1977).

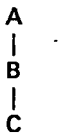
The compounds are therefore indicated for use as anti-depressants, e.g. for the treatment of somatogenic, endogenous and psychogenous depressions.

For the above-mentioned uses as anti-tremor, anti-rigor, myotonolytic and muscle relaxant, tranquillizing and sedative, and antidepressant agents an indicated daily dosage is from about 0.2 mg to about 200 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.05 mg to about 100 mg, or in sustained release form.

The compounds of the invention in free form or in the form of their pharmaceutically acceptable salts may be administered alone or in suitable dosage forms. The present invention also provides a pharmaceutical composition comprising a compound of the invention in free form or in salt, preferably acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions, e.g. a solution or a tablet, may be produced according to known methods.

CLAIMS

1. A process for the production of a compound of formula I



I

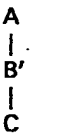
wherein

A is an optionally substituted 2,1,3-benzothiadiazole or 2,1,3-benzoxadiazole moiety,

B is a trisubstituted amino group and

C is an optionally 1-substituted 4,5-dihydro-1H-imidazol-2-yl or an optionally 3-substituted 3,4,5,6-tetrahydropyrimidin-2-yl moiety, which comprises

a) appropriately substituting a corresponding compound of formula II

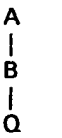


II

wherein

A and C are as defined above and B′ is a secondary amino group or

b) reacting a corresponding compound of formula III

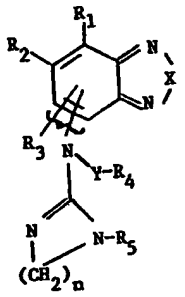


III

wherein

A and B are as defined above and Q is a group capable of cyclization with a diamine, with a corresponding, optionally 1-substituted ethylene or propylene diamine.

2. A process according to claim 1 for the production of a compound of formula Ia



Ia

wherein

n is 2 or 3,

X is oxygen or sulfur,

Y is a bond or oxygen,

R_1, R_2 and R_3 independently are hydrogen, halogen of atomic number of from 9 to 53, cyano, hydroxy, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or alkylthio of 1 to 4 carbon atoms,

R_4 is

i) alkyl of 1 to 6 carbon atoms optionally monosubstituted by hydroxy or halogen of atomic number of from 9 to 53 and wherein the hydroxy or halogen moiety is separated from Y by at least 2 carbon atoms; alkenyl of 3 to 6 carbon atoms optionally monosubstituted by halogen of atomic number of from 9 to 53 and wherein the double bond and the halogen moiety are separated from Y by at least 2 carbon atoms; alkinyl of 3 to 6 carbon atoms wherein the triple bond is separated from Y by at least 2 carbon atoms; cycloalkyl of 3 to 7 carbon atoms; cycloalkylalkyl of 3 to 7 carbon atoms in the cycloalkyl moiety and of 1 to 4 carbon atoms in the alkyl moiety thereof;

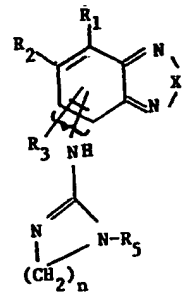
ii) 2,2,5,5-tetraalkylpyrrolidin-1-ylalkyl or 2,2,6,6-tetraalkylpiperidin-1-ylalkyl independently of 1 to 4 carbon atoms in each of the alkyl moieties of the pyrrolidine or piperidine moiety, of 2 to 5 carbon atoms in the alkyl moiety bound to Y and wherein the nitrogen atom of the pyrrolidine or piperidine moiety is separated from Y by at least 2 carbon atoms; furanylalkyl, thienylalkyl or pyridylalkyl each of 1 to 4 carbon atoms in the alkyl moiety thereof; or morpholin-1-ylalkyl of 2 to 5 carbon atoms in the alkyl moiety thereof and wherein the nitrogen atom of the morpholine moiety is separated from Y by at least 2 carbon atoms:

iii) phenylalkyl of 7 to 11 carbon atoms, phenoxyalkyl of 8 to 12 carbon atoms wherein the oxygen atom is separated from Y by at least 2 carbon atoms, phenylcarbonylalkyl of 8 to 12 carbon atoms, phenylalkoxyalkyl of 1 to 4 carbon atoms in the alkoxy and of 2 to 5 carbon atoms in the alkyl moiety thereof and wherein the oxygen atom is separated from Y by at least 2 carbon atoms, phenylalkenyl of 9 to 13 carbon atoms wherein the double bond is separated from Y by at least 2 carbon atoms, phenylalkinyl of 9 to 13 carbon atoms wherein the triple bond is separated from Y by at least 2 carbon atoms, all the phenyl rings in the six above-mentioned substituents optionally being mono- or independently di-substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 53 or, when Y is a bond, alternatively or additionally also by hydroxy; or

iiii) when Y is oxygen, additionally hydrogen, and R_5 is hydrogen or alkyl of 1 to 4 carbon atoms,

which comprises

a) appropriately substituting the bridging nitrogen atom in a corresponding compound of formula IIa

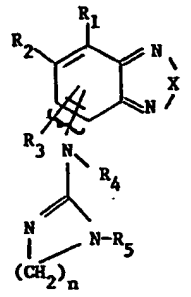


IIa

wherein

n, X, R_1, R_2, R_3 and R_5 are as defin d abov or

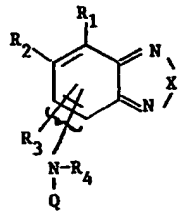
b) for the production of a compound of formula Iaa,



Iaa

wherein

n, X and R_1 to R_5 are as defined above, reacting a corresponding compound of formula IIIa



IIIa

wherein

X and R_1 to R_4 are as defined above and Q is as defined in claim 1, with a corresponding compound of formula IV

$$H_2N—(CH_2)_n—NHR_5 \qquad IV$$

wherein n and R_5 are as defined above.

3. A process for the production of a compound of formula I, as defined in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

4. A compound of formula I, as defined in claim 1, whenever produced by a process according to claim 1 to 3.

5. A compound of formula I, as defined in claim 1.

6. A compound of claim 5 of formula Ia, as defined in claim 2.

7. A compound of claim 6 of formula Ia wherein X is sulfur.

8. A compound of claim 6 of formula Ia wherein Y is a bond.

9. A compound of claim 6 of formula Ia wherein Y is oxygen.

10. A compound of claim 6 of formula Ia wherein R_1 and R_2 are hydrogen.

11. A compound of claim 6 of formula Ia wherein R_3 is halogen.

12. A compound of claim 6 of formula Ia wherein the nitrogen atom carrying Y—R_4 is bound at the 4 position of the 2,1,3-benzothiadiazole or 2,1,3-benzoxadiazole ring.

13. A compound of claim 6 of formula Ia wherein R_4 has significance i).

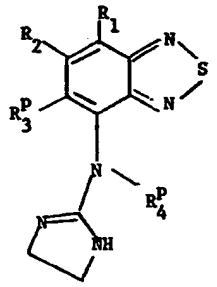
14. A compound of claim 6 of formula Ia wherein R_4 has significance iii).

15. A compound of claim 6 of formula Ia wherein R_5 is hydrogen.

16. A compound of claim 6 of formula Ia wherein R_4 is alkenyl.

17. A compound of claim 6 of formula Ia wherein R_4 is optionally substituted phenylalkyl, phenoxyalkyl, phenylalkoxyalkyl or phenylalkenyl.

18. A compound of claim 5 of formula Ipa,



Ipa

wherein

R_1 and R_2 are as defined in claim 2

R_3^p has the significance indicated in claim 2 for R_3 and

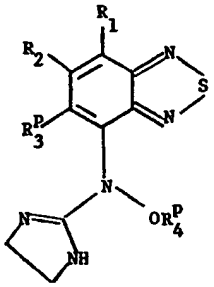
R_4^p is

i) alkyl of 1 to 6 carbon atoms; alkenyl of 3 to 6 carbon atoms wherein the double bond is separated from the nitrogen atom by at least 2 carbon atoms; 2-chloro-2-propenyl; alkinyl of 3 to 6 carbon atoms wherein the triple bond is separated from the nitrogen atom by at least 2 carbon atoms; cycloalkyl of 3 to 7 carbon atoms; cycloalkylalkyl of 3 to 6 carbon atoms in the cycloalkyl moiety and of 1 to 4 carbon atoms in the alkyl moiety thereof, the total number of carbon atoms not exceeding 7;

ii) thienylmethyl, 2-furanylmethyl or pyridylmethyl; or

iii) benzyl or cinnamyl.

19. A compound of claim 6 of formula Ipb,



Ipb

wherein

R_1 and R_2 are as defined in claim 2 and R_3^p and R_4^p are as defined in claim 18.

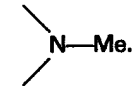
20. The compound of claim 5 which is N-allyl-5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine.

21. The compound of claim 5 which is 5-chloro-N-hydroxy-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine.

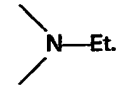
22. The compound of claim 5 which is 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-N-(2-phenoxyethoxy)-2,1,3-benzothiadiazol-4-amine.

23. A compound of claim 5 of formula I wherein A is 5-chloro-2,1,3-benzothiadiazol-4-yl and C is 4,5-dihydro-1H-imidazol-2-yl.

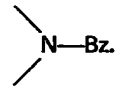
24. The compound of claim 23 wherein B is



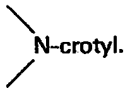
25. The compound of claim 23 wherein B is



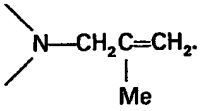
26. The compound of claim 23 wherein B is



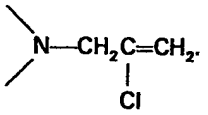
27. The compound of claim 23 wherein B is



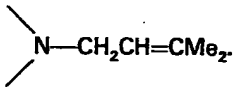
28. The compound of claim 23 wherein B is



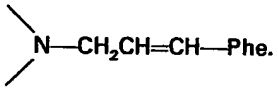
29. The compound of claim 23 wherein B is



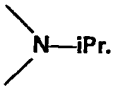
30. The compound of claim 23 wherein B is



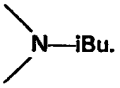
31. The compound of claim 23 wherein B is



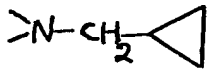
32. The compound of claim 23 wherein B is



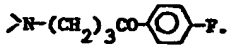
33. The compound of claim 23 wherein B is



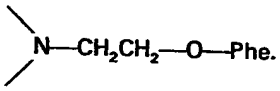
34. The compound of claim 23 wherein B is



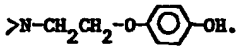
35. The compound of claim 23 wherein B is



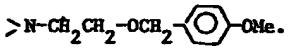
36. The compound of claim 23 wherein B is



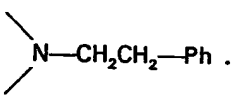
37. The compound of claim 23 wherein B is



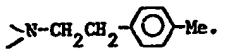
38. The compound of claim 23 wherein B is



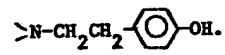
39. The comp und of claim 23 wherein B is



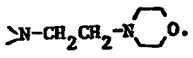
40. The compound f claim 23 wh rein B is



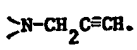
41. The compound of claim 23 wherein B is



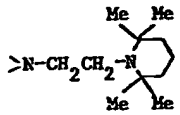
42. The compound of claim 23 wherein B is



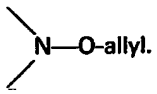
43. The compound of claim 23 wherein B is



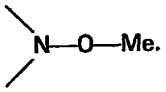
44. The compound of claim 23 wherein B is



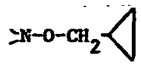
45. The compound of claim 23 wherein B is



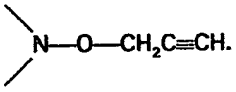
46. The compound of claim 23 wherein B is



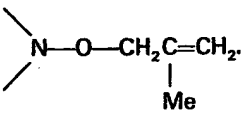
47. The compound of claim 23 wherein B is



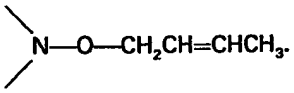
48. The compound of claim 23 wherein B is



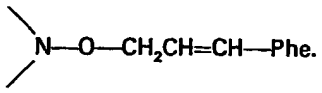
49. The compound of claim 23 wherein B is



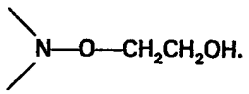
50. The compound of claim 23 wherein B is



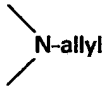
51. The compound of claim 23 wherein B is



52. The compound of claim 23 wherein B is



53. A compound of claim 5 of formula I wherein B is



and C is 4,5-dihydro-1H-imidazol-2-yl.

54. The compound of claim 53 wherein A is 5-chloro-7-methyl-2,1,3-benzothiadiazol-4-yl.

55. The compound of claim 53 wherein A is 4-methyl-2,1,3-benzothiadiazol-5-yl.

56. The compound of claim 53 wherein A is 4-bromo-2,1,3-benzothiadiazol-5-yl.

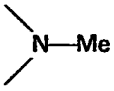
57. The compound of claim 53 wherein A is 7-chloro-5-methyl-2,1,3-benzothiadiazol-4-yl.

58. The compound of claim 53 wherein A is 5-methyl-2,1,3-benzothiadiazol-4-yl.

59. The compound of claim 53 wherein A is 5-methyl-2,1,3-benzoxadiazol-4-yl.

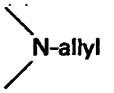
60. The compound of claim 53 wherein A is 5,7-dimethyl-2,1,3-benzoxadiazol-4-yl.

61. The compound of claim 5 wherein A is 5-chloro-2,1,3-benzothiadiazol-4-yl, B is



and C is 4,5-dihydro-1H-1-methylimidazol-2-yl.

62. The compound of claim 5 wherein A is 5-chloro-2,1,3-benzothiadiazol-4-yl, B is



and C is 4,5-dihydro-1H-1-methylimidazol-2-yl.

63. A compound of any one of claims 5 to 62 in free form.

64. A compound of any one of claims 5 to 62 in salt form.

65. A compound of any one of claims 5 to 62 in acid addition salt form.

66. A pharmaceutical composition which comprises a compound of any one of claims 5 to 62 in free form or in pharmaceutically acceptable salt form in association with a pharmaceutical carrier or diluent.

67. A method of treating cardiac disorders, tremor, rigor, spastic conditions, of relaxing muscles, f tranquillizing or sedating subjects or of treating depressions which comprises administering to an animal in need of such treatment a therapeutically effective amount of a compound in claim 5.

68. A compound of claim 5 for use as a pharmaceutical.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained